# PATENT COOPERATION TREATY

# PCT



## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference<br>VM/gf G69414 | **FOR FURTHER ACTION** | See Form PCT/IPEA/416 |
|---|---|---|
| International application No.<br>PCT/EP2005/000522 | International filing date *(day/month/year)*<br>20.01.2005 | Priority date *(day/month/year)*<br>21.01.2004 |

International Patent Classification (IPC) or national classification and IPC
INV. A61K31/202 A61P25/28 A61P25/08 A61P25/18

Applicant
BRUZZESE, Tiberio

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 4 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☒ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

| | | |
|---|---|---|
| ☒ | Box No. I | Basis of the report |
| ☐ | Box No. II | Priority |
| ☒ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☐ | Box No. VII | Certain defects in the international application |
| ☐ | Box No. VIII | Certain observations on the international application |

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 27.10.2005 | 24.05.2006 |

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**Box No. I Basis of the report**

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   **Description, Pages**

   1-12 as originally filed

   **Claims, Numbers**

   1-21 received on 27.10.2005 with letter of 26.10.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☒ the claims, Nos. 1-21
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 26-28

because:

☒ the said international application, or the said claims Nos. with respect to Industrial Applicability relate to the following subject matter which does not require an international preliminary examination *(specify)*:

**see separate sheet**

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*.

☐ no international search report has been established for the said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 4,5,8,9,15,16,24,25 |
| | No: | Claims | 1-3,6,7,10-14,17-23,26-28 |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1-28 |
| Industrial applicability (IA) | Yes: | Claims | 1-25 |
| | No: | Claims | |

2. Citations and explanations (Rule 70.7):

**see separate sheet**

**Re Item I:**

1. The amendments filed with the letter dated 26.20.05 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT. The amendments concerned are the following:
the provisos of claim 1 that:
when the composition comprises b), arachidonic acid is not added thereto; and
when the composition comprises c), it does not comprise 10 to 40% by weight of reducing/antioxidant vitamins or provitamins.

   These provisos have no basis in the application as filed and are therefore considered to introduce new subject-matter.

   **Consequently the examination will be based on the originally filed set of claims.**

**Re Item III:**

2. Claims 26-28 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

**Re Item V:**

3. The documents considered in the present processing are consecutively numbered D1-D9; this numbering results from the citations D1-D9 found in the International Search Report (ISR) of the corresponding PCT application. It will be adhered to in the rest of the procedure. The cited passage(s) for each citation will be considered unless otherwise specified.

4. The application refers to the use of a composition comprising either a) alpha-linolenic acid (ALA, C18:3 n-3) or b) docosahexaenoic acid (DNA, C22:6 n-3) or c) DNA in admixture with eicosapentaenoic acid (EPA, C20:5 n-3), in a ratio of 1:0.5 to 1:1.7, respectively, and/or the pharmaceutically acceptable derivatives and/or precursors thereof either a) or b) or c) being in a concentration not lower than 70% by weight of the total fatty acids weight in the composition, for the

preparation of a drug for the prevention and/or treatment of the disturbances of the central nervous system (CNS) such as epilepsy, schizophrenia, bipolar (manic-depressive illness) and unipolar (major depression) psychiatric disorders, and by degenerative Alzheimer's disease and related forms of dementia.

5. Novelty, Art. 33(2) PCT

5.1 D1 discloses a pharmaceutical composition comprising omega-3 fatty acids for the treatment of central and peripheral nervous system disease. Example 4 relates to DHA ethylester together with EPA ethylester in a ration of 1:1.
Thus, D1 is considered novelty destroying for the subject-matter of claims 1,2, 10-13, 18-23 and 26.
D2 describes a method of treating the negative syndrome of schizophrenia by the coadministration of arachidonic acid and docosahexaenoic acid in a ratio of 20:1 to 1:20.
Thus, D2 is considered novelty destroying for the subject-matter of claims 1-3, 6, 7, 11-14, 17-23 and 26-28.
D3 focuses on omega-3 fatty acid supplementation in schizophrenic patients. Patients were given 1g capsules supplied with 171mg of EPA and 114mg of DHA (ratio of 1,5:1).
D3 is considered novelty destroying for the subject-matter of claims 1-3,6,7, 11-13, 19-23 and 26-28.

5.2 The subject-matter of claims 4,5,8,9,15,16,24 and 25 is considered formally novel over the cited prior art within the meaning of Article 33(2) PCT.
Claims 4 and 5 differ from D1-D3 that a more specific form of epilepsy is claimed. Manic-depressive syndrome and Alzheimer's disease as claimed in claims 8 and 9 are not disclosed in D1 - D3.
Claim 15 comprises at least two other n-3 and/or n-6 fatty acids and claim 16 defines the concentration of that other fatty acid of lower or equal to 30%.
Claims 24 and 25 discloses the coadministration of at least another drug effective for the prevention or treatment of CNS disturbances.

6. Inventive Step, Article 33(3) PCT
The problem underlying the present application is the provision of a composition for

the prevention or treatment of CNS disturbances.
The posed solution is a composition according to claim 1.
As it can be seen from the cited prior art, the use of polyunsaturated fatty acid for the prevention or treatment of CNS disturbances has been intensively studied.
D4, D5 and D9 relate to the treatment of epilepsy and D6-D8 to the treatment of schizophrenia.
The embodiments encompassed by claims 4,5,15,16 24 and 25 seem to be obvious modifications to the known therapeutic use of such compositions which cannot justify an inventive merit.

The use of such a composition for the treatment of manic-depressive syndrome and Alzheimer's disease is not disclosed in the cited prior art.
However, all the examples provided in the application relate to epilepsy or schizophrenia.
If the experimental data presented in the present application can be generalized to these specific diseases than this approach is also justified for the prior art.

Thus, in other words either it must be considered that the application does not show that the problem has been solved for manic-depressive syndrome and Alzheimer's disease or this use is obvious for the skilled man by the disclosure of the cited prior art.

Therefore, it seems that the subject-matter of claims 1-28 lack inventive step within the meaning of Article 33(3) PCT.

CLAIMS

1. Use of a composition comprising either

a) alpha-linolenic acid (ALA, C18:3 n-3) and/or the pharmaceutically acceptable derivatives and/or precursors thereof; or

b) docosahexaenoic acid (DHA, C22:6 n-3) and/or the pharmaceutically acceptable derivatives and/or precursors thereof; or

c) DHA in admixture with eicosapentaenoic acid (EPA, C20:5 n-3) , in a ratio of 1:0.5 to 1:1.7, respectively, and/or the pharmaceutically acceptable derivatives and/or precursors thereof;

either a) or b) or c) being in a concentration not lower than 70% by weight of the total fatty acids weight in the composition, for the preparation of a drug for the prevention and/or treatment of the psychiatric disturbances of the central nervous system (CNS) selected from the group consisting of schizophrenia, manic-depressive syndrome, major depression, and Alzheimer's disease;

with the provisos that:

when the composition comprises b), arachidonic acid is not added thereto; and

when the composition comprises c), it does not comprise 10 to 40% by weight of reducing/antioxidant vitamins or provitamins.

~~CLAIMS~~

~~1. Use of a composition comprising either~~

a) alpha-linolenic acid (ALA, C18:3 n-3) and/or the pharmaceutically acceptable derivatives and/or precursors thereof; or

b) docosahexaenoic acid (DHA, C22:6 n-3) and/or the pharmaceutically acceptable derivatives and/or precursors thereof; or

c) DHA in admixture with eicosapentaenoic acid (EPA, C20:5 n-3) , in a ratio of 1:0.5 to 1:1.7, respectively, and/or the pharmaceutically acceptable derivatives and/or precursors thereof;

either a) or b) or c) being in a concentration not lower than 70% by weight of the total fatty acids weight in the composition, for the preparation of a drug for the prevention and/or ~~treatment of the disturbances of the central nervous system (CNS).~~

~~2. Use according to claim 1, wherein the disturbances of CNS are neurological and/or~~ psychiatric disturbances.

3. Use according to claim 1 or 2, wherein the disturbances of CNS are epilepsy, schizophrenia, manic-depressive syndrome, ~~major~~ depression, and Alzheimer's disease.

4. Use according to the previous claim, wherein epilepsy shows partial and/or generalized seizures.

~~5. Use according to claim 3 or 4, wherein epilepsy shows simple and/or complex seizures.~~

2 ~~6~~. Use according to claim ~~3~~ 1, wherein schizophrenia shows negative and/or positive symptoms.

3. ~~7~~. Use according to claim ~~3 or 6~~ 1 or 2, wherein schizophrenia is paranoid, catatonic, disorganised or undifferentiated schizophrenia.

4. ~~8~~. Use according to ~~claim 3~~ any of the previous claims, wherein the manic-depressive syndrome and major depression include disorders of mood, behaviour and autonomic functions correlated to activity, sleep and appetite.

5 ~~9~~. Use according to claim ~~3~~ 1, wherein the Alzheimer's disease includes the various related forms of dementia.

6. ~~10~~. Use according to any of the previous claims, wherein the ratio of DHA to EPA in c) is of 1:0.9 to 1:1.5.

7. ~~11~~. Use according to any of the previous claims, wherein the concentration of either a) or b) or c) is of 75% to 95% by weight of the total fatty acids weight in the composition.

8. ~~12~~. Use according to any of the previous claims, wherein the concentration of either a) or b) or c) is of 80% to 90% by weight of the total fatty acids weight in the composition.

9. ~~13~~. Use according to any of the previous claims, wherein the concentration of either a) or b)

or c) is of 85% by weight of the total fatty acids weight in the composition.

10. ~~14~~. Use according to any of the previous claims, wherein the composition comprises at least another n-3 and/or n-6 polyunsaturated and/or monounsaturated and/or saturated fatty acid.

11. ~~15~~. Use according to the previous claim, wherein the composition comprises at least two other n-3 and/or n-6 polyunsaturated and/or monounsaturated and/or saturated fatty acids, in any ratio among themselves.

12. ~~16~~. Use according to claim ~~14 or 15~~ 10 or 11, wherein the other n-3 and/or n-6 polyunsaturated and/or monounsaturated and/or saturated fatty acids are in a concentration of lower or equal to 30%.

13. ~~17~~. Use according to any of the previous claims, wherein the derivatives of ALA, DHA and EPA are selected from the group consisting of their $C_1$-$C_3$ alkyl esters, glyceride mono-, di-, tri-esters, salts with pharmaceutically acceptable bases, whereas the precursors of ALA, DHA and EPA are the compounds able to lead to them through *in vivo* transformations.

14. ~~18~~. Use according to any of the previous claims, wherein the drug comprises essentially DHA ethyl ester and EPA ethyl ester.

15. ~~19~~. Use according to any of the previous claims, wherein the drug is administered by oral route.

16. ~~20~~. Use according to any of the previous claims, wherein the drug is in the form of soft gelatine capsules.

17. ~~21~~. Use according to any of the previous claims, wherein the drug is administered at the dose of 0.1-5 g/day.

18. ~~22~~. Use according to any of the previous claims, wherein the drug is administered at the dose of 0.3-3 g/day.

19. ~~23~~. Use according to any of the previous claims, wherein the drug is administered at the dose of 1-2 g/day.

20. ~~24~~. Use according to any of the previous claims, wherein the drug is administered separately, as a coadjuvant or an auxiliary drug, from at least another drug effective for the prevention and/or treatment of the disturbances of CNS.

21. ~~25~~. Use according to any of the previous claims, wherein the drug comprises at least another drug effective for the prevention and/or treatment of the disturbances of CNS.

~~26. A method for prevention and/or treatment of CNS disturbances in a mammal in need~~ thereof comprising administering to the mammal a therapeutically ~~effective~~ dose of a drug as defined in any of the previous claims.

27. A method ~~according to the previous claim, wherein the therapeutically effective dose ranges from about 2 to 60 mg/kg of the mammal body weight per day.~~

~~28. A method according to claim 26 or 27, wherein the CNS disturbances are epilepsy, schizophrenia, manic-depressive syndrome, major depression and Alzheimer's disease.~~